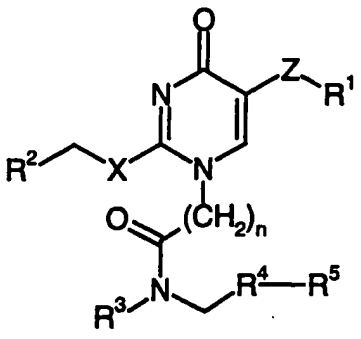
Claims

1. A compound of formula (I):



(I)

in which:

R^1 is an aryl or heteroaryl group, optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-18)}$alkyl, $C_{(1-18)}$alkoxy, $C_{(1-18)}$alkylthio, aryl$C_{(1-18)}$alkoxy, hydroxy, halogen, CN, COR^6, carboxy, $COOR^6$, $CONR^9R^{10}$, NR^6COR^7, $SO_2NR^9R^{10}$, $NR^6SO_2R^7$, NR^9R^{10}, mono to perfluoro-$C_{(1-4)}$alkyl and mono to perfluoro-$C_{(1-4)}$alkoxy, or, as a single substituent, optionally in combination with a further substituent as hereinbefore defined, CH_2COOH or a salt thereof, CH_2COOR^8, $CH_2CONR^9R^{10}$, CH_2CN, $(CH_2)_mNR^9R^{10}$, $(CH_2)_mOH$ or $(CH_2)_mOR^6$ where m is an integer from 1 to 3;

R^2 is an aryl or heteroaryl group, optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-18)}$alkyl, $C_{(1-18)}$alkoxy, $C_{(1-18)}$alkylthio, aryl$C_{(1-18)}$alkoxy, hydroxy, halogen, CN, COR^6, carboxy, $COOR^6$, $CONR^9R^{10}$, NR^6COR^7, $SO_2NR^9R^{10}$, $NR^6SO_2R^7$, NR^9R^{10}, mono to perfluoro-$C_{(1-4)}$alkyl, mono to perfluoro-$C_{(1-4)}$alkoxy, and aryl$C_{(1-4)}$alkyl;

R^3 is hydrogen or $C_{(1-4)}$alkyl which may be unsubstituted or substituted by hydroxy, OR^6, COR^6, carboxy, $COOR^6$, $CONR^9R^{10}$, NR^9R^{10}, mono- or di-(hydroxy$C_{(1-6)}$alkyl)amino or N-hydroxy$C_{(1-6)}$alkyl-N-$C_{(1-6)}$alkyl amino;

R^4 is an aryl or a heteroaryl ring optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-18)}$alkyl, $C_{(1-18)}$alkoxy, $C_{(1-18)}$alkylthio, aryl$C_{(1-18)}$alkoxy, hydroxy, halogen, CN, COR^6, carboxy, $COOR^6$, $CONR^9R^{10}$, NR^6COR^7, $SO_2NR^9R^{10}$, $NR^6SO_2R^7$, NR^9R^{10}, mono to perfluoro-$C_{(1-4)}$alkyl and mono to perfluoro-$C_{(1-4)}$alkoxy;

R^5 is an aryl ring which is further optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-18)}$alkyl, $C_{(1-18)}$alkoxy, $C_{(1-18)}$alkylthio, aryl$C_{(1-18)}$alkoxy, hydroxy, halogen, CN, COR^6, carboxy, $COOR^6$, $CONR^9R^{10}$, NR^6COR^7, $SO_2NR^9R^{10}$, $NR^6SO_2R^7$, NR^9R^{10}, mono to perfluoro-$C_{(1-4)}$alkyl and mono to perfluoro-$C_{(1-4)}$alkoxy;

R^6 and R^7 are independently hydrogen or $C_{(1-20)}$alkyl, for instance $C_{(1-4)}$alkyl (e.g. methyl or ethyl);

R^8 is $C_{(1-4)}$alkyl or a pharmaceutically acceptable *in vivo* hydrolysable ester group;

R^9 and R^{10} which may be the same or different is each selected from hydrogen, $C_{(1-12)}$alkyl, CH_2R^{11}, $CHR^{12}CO_2H$ or a salt thereof, or R^9 and R^{10} together with the nitrogen to which they are attached form a 4- to 7-, preferably 5- to 7-, membered ring optionally containing one or more further heteroatoms selected from oxygen, nitrogen and sulphur, and optionally substituted by one or two

substituents selected from hydroxy, oxo, $C_{(1-4)}$alkyl, $C_{(1-4)}$alkylCO, aryl, e.g. phenyl, or aralkyl, e.g benzyl, for instance morpholine or piperazine;

R^{11} is COOH or a salt thereof, $COOR^8$, $CONR^6R^7$, CN, CH_2OH or CH_2OR^6;

R^{12} is an amino acid side chain such as CH_2OH from serine;

n is an integer from 1 to 4, preferably 1 or 3;

X is O or S; and

Z is $CR^{13}R^{14}$ where R^{13} and R^{14} are each hydrogen or $C_{(1-4)}$alkyl, or R^{13} and R^{14} together with the intervening carbon atom form a $C_{(3-6)}$cycloalkyl ring.

2. A compound of formula (I) as claimed in claim 1 in which Z is CH_2.

3. A compound of formula (I) as claimed in claim 1 or 2 in which R^1 is an aryl group selected from phenyl and naphthyl or a heteroaryl group which comprises a 5- or 6- membered, monocyclic heteroaryl group comprising 1 or 2 nitrogen heteroatoms.

4. A compound of formula (I) as claimed in any one of claims 1 to 3 in which R^1 is pyrimidyl optionally substituted by 1 or 2 substituents selected from oxo, aryl$C_{(1-4)}$alkyl, $C_{(1-6)}$alkyl, $C_{(3-6)}$cycloalkyl, hydroxy, $C_{(1-4)}$alkoxy, carboxy$C_{(1-6)}$alkyl, $C_{(1-6)}$alkylcarboxy$C_{(1-6)}$alkyl, di-$C_{(1-6)}$alkylamino, and morpholino; or pyrazolyl optionally substituted by $C_{(1-6)}$alkyl.

5. A compound as claimed in claim 4 in which ZR^1 is pyrimid-5-ylmethyl optionally substituted by 2-methoxy, 2-trifluoromethyl, 2-(4-morpholino) or 2-dimethylamino; 2-oxo-pyrimid-5-ylmethyl or 1-methyl-4-pyrazolylmethyl.

6. A compound of formula (I) as claimed in any one of claims 1 to 6 in which X is S.

7. A compound of formula (I) as claimed in any one of claims 1 to 6 in which R^2 is an aryl group selected from phenyl and naphthyl or a heteroaryl group selected from pyridyl, pyrimidinyl, pyrazolyl, furanyl, thienyl, thiazolyl, quinolyl, benzothiazolyl, pyridazolyl and pyrazinyl.

8. A compound of formula (I) as claimed in claim 7 in which R^2 is phenyl optionally substituted by halogen

9. A compound of formula (I) as claimed in any one of claims 1 to 8 in which R^3 is selected from hydrogen; and methyl, ethyl and propyl, optionally substituted by amino, $C_{(1-3)}$alkylamino, di $C_{(1-3)}$alkylamino, hydroxy$C_{(1-3)}$alkylamino, hydroxy, $C_{(1-3)}$alkoxy, carboxy, $C_{(1-3)}$alkylcarboxy, and heterocycyl.

10. A compound of formula (I) as claimed in any one of claims 1 to 9 in which R^4 is selected from phenyl optionally substituted by halogen; thiophene; pyridine; and pyrimidine.

11. A compound of formula (I) as claimed in any one of claims 1 to 10 in which R^5 is phenyl optionally substituted by halogen, trifluoromethyl, or trifluoromethoxy.

12. A compound of formula (I) as claimed in claim 10 or 11 in which R^4 and R^5 together form a 4-(phenyl)phenyl substituent in which the remote phenyl ring may be optionally substituted by halogen or trifluoromethyl.

13. A compound of formula (I) as claimed in claim 1 and as named in any one of Examples 1 to 157.

14. A compound of formula (I) as claimed in claim 13 selected from:
1-(N-Methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one;
1-(N-Methyl-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one;
1-(N-(2-Dimethylaminoethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one;
1-(N-Methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-(4-morpholino)pyrimid-5-ylmethyl)pyrimidin-4-one;
1-(N-(2-(dimethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one;
1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one;
1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one;
1-(N-(2-(1-Piperidino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one bitartrate;
1-(N-(Carboxymethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one sodium salt; and
1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one or a pharmaceutically acceptable salt thereof, including the hydrochloride, bitartrate, citrate and tosylate salts.

15. A pharmaceutical composition comprising a compound of formula (I) as claimed in any one of the preceding claims and a pharmaceutically acceptable carrier.

16. A compound of formula (I) as claimed in claim 1 for use in therapy.

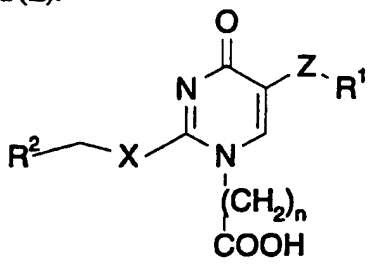
17.. The use of a compound of formula (I) as claimed in claim 1 for the manufacture of a medicament for treating atherosclerosis.

18. A method of treating a disease state associated with activity of the enzyme Lp-PLA_2 which method involves treating a patient in need thereof with a therapeutically effective amount of a compound of formula (I) as claimed in claim 1.

19. A method of treating atherosclerosis which method comprises administering t a patient in need thereof an effective amount of a compound of formula (I) as claimed in claim 1 and a statin.

20. A process for preparing a compound of formula (I) as defined in claim 1 which process comprises:

(a) reacting a compound of formula (II):



(II)

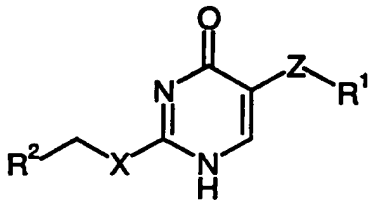
in which X, Y, Z, R^1 and R^2 are as defined in claim 1,
with a compound of formula (III):

$$R^5\text{-}R^4\text{-}CH_2NHR^3$$

(III)

in which R^3, R^4 and R^5 are as defined in claim 1; under amide forming conditions;

(b) reacting a compound of formula (IV):



(IV)

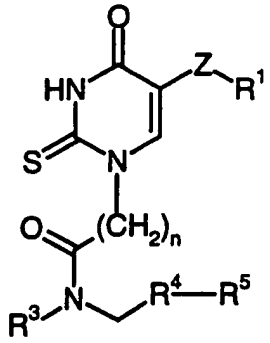
in which X, Z, R^1 and R^2 are as defined in claim 1,
with a compound of formula (V):

$$R^5\text{-}R^4\text{-}CH_2NR^3\text{-}CO\text{-}(CH_2)_n\text{-}L^1$$

(V)

in which n, R^3, R^4 and R^5 are as defined in claim 1, and L^1 is a leaving group such as halogen;
in the presence of a base such as a secondary or tertiary amine, in an inert solvent;

(c) when X is S, reacting a compound of formula (VI):



(VI)

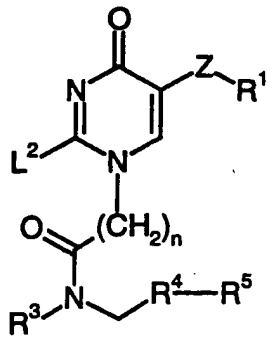
in which n, Z, R^1, R^3, R^4 and R^5 are as defined in claim 1,
with a compound of formula (VII):

$$R^2\text{-}CH_2\text{-}L^1$$

(VII)

in which R^2 and L^1 are as defined in claim 1,
in the presence of a base such as a secondary or tertiary amine, in an inert solvent; or

(d) when X is O, reacting a compound of formula (VIII):



(VIII)

in which n, Z, R^1, R^3, R^4 and R^5 are as defined in claim 1, and L^2 is a leaving group,
with a compound of formula (IX):

$$R^2\text{-}CH_2\text{-}OH$$

(IX)

in which R^2 is as defined in claim 1,
in the presence of a base, in an inert solvent.